Ethics and Clinical trials
EU approach

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The view I express are my own and do not necessarily reflect those of the European Commission.

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EU Policy

- In his main speech after his re-election as President of the European Commission for a new five-year term President Barroso said: " I will redouble my efforts to make an ambitious Europe happen. A Europe that puts people at the heart of the policy agenda and **projects European values** and interests in the world.
- This ntion is also incorpotrated in **President Barroso political guidelines for the mandate of the next European Commission** to the president of the European Parliament setting the objectives that president Barroso believes should inspire a political partnership between the Commission and the Parliament for the next five years.

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- The defence of human rights and a justice system based on the full respect of human dignity is a key part of our shared European values" Jerzy Buzek, European Parliament President (10 October, 2009)

- "Europe is a community of Values". Van Rompuy, First European Council President, 19 November 2009

- "My political guidelines for the Commission's next mandate stress the idea that Europe's actions must be based on its values". President Barroso, European values in the new global governance, 14 October 2009

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Legislative domain

- Issues of bioethics in the **legislative sphere** cover very many disparate areas of policy; from **clinical trials** (Directive 2001/20/EC) to **patents** (Directive 94/48); from **data protection** (Directive 95/46) to **research** (FP) or production of **medicinal products** (Directive 2001/83/EC and others, e.g. 2003/63/EC); from **animals used for experimental** and other scientific purposes (Directive 86/609/EC) to **animal welfare** (Protocol to the Amsterdam Treaty) etc.
- The list of Community regulations also includes applications of **biotechnology**, **information technologies, security and surveillance, ICT** and several areas of **biomedical sciences**.

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- **The new Article 168 Treaty on the Functioning of the European Union: "*Community action shall be directed towards improving public health, preventing, human illness and diseases, and obviating sources of danger to human health*" and this by "*encouraging cooperation between the member States*" *and* "*lending support to their action*"."**
- **Article 168 strongly reasserts the principle of subsidiarity. The Union shall fully respect Member States responsibilities for the definition of health policies and organising, delivering health services and medical care.**

- A key area of potential impact on health policy is the inclusion of the Charter of Fundamental Rights into binding law for most Member States. Many of the articles have potential implications for health policy. Article 1 on human dignity may be said to be the basis of all elements of the right to health, as well as Article 3 on the integrity of the person. Article 2 safeguards the right to life. Article 8 on the protection of personal data may be relevant to data that medical professionals may hold on their patients, data with respect to medical research and patients' entitlement to view their medical records. Article 10, on the freedom of conscience, belief and religion, and Article 26 on integration of persons with disabilities may also be important

Clinical Trials in Europe

Legislation

- Directive 2001/20/EC… on… Clinical Trials…
- Directive 2003/94/EC Good Manufacturing Practice
- Directive 2005/28/EC on Good Clinical Practice*

Soft law

- Guidance on application to Competent Authorities and to Ethics Committees
- Guidance on collection and reporting of SUSARs (Suspected Unexpected Serious Adverse Reactions in clinical trials)
- Guidance on the **Eudravigilance** database (containing post-marketing ICSRs (Individual Case Safety Reports) and SUSARs)
- Guidance on the **EUDRACT** Database (covering all clinical trials conducted within the Community, to be used by authorities)
- Annex 13 of the EU Guide to GMP

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Ethical principles governing the conduct of clinical trials in the EU

- **Research may only be undertaken if the research project has been approved by an ethics committee** (or other bodies authorised to review clinical research on human beings) after independent examination of its scientific merit, including assessment of the importance of the aim of research, and multidisciplinary review of its ethical acceptability. Ethics committees have to be pluralist, multidisciplinary and independent.
- The **ethics committee must be independent of the research team and sponsor**, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review, and should be declared.

Ethical principles governing the conduct of clinical trials in the EU

- Where a clinical trial is to be conducted in countries that have limited frameworks for ethical review or regulatory oversight, the sponsor should consider submitting the study protocol for ethical and scientific review to an ethics committee(s) that operates within an established regulatory framework with ethical standards equivalent to those applying in the EU, in addition to doing to in the country concerned by the trial.
- The deliberations and conclusions of that committee(s) should be made available to the local ethics committee and regulatory authority, making clear to what extent the committee has considered the location and circumstances in which the trial is to be conducted. Such an approach does not substitute for the need to apply to, and follow the requirements of, a local ethics committee or to submit to the regulatory authority of the country where the trial is to be conducted.

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Ethical principles governing the conduct of clinical trials in the EU

- The local ethics committee(s) and competent authority in the country where the trial is to be conducted should review the trial, ensuring that the proposed research is ethical, **takes into account the local conditions**, that the local sites are suitable and that circumstances and arrangements for the conduct of the research are appropriate for that country and the study population concerned.
- In multicentre studies, **a central ethics committee** could **review the study** from a scientific and ethical standpoint, and **the local ethics committee could verify** the practicability of the study in their communities, including the infrastructures, the state of training, and ethical considerations of local significance.

The Clinical Trials Directive

- The Clinical Trials Directive has been subject to two major criticisms: The increased administrative requirements for clinical trials and the divergent application of the Clinical Trials Directive in the Member States.
- An impact assessment has been announced in the COM Communication on the Pharmaceutical Sector of Dec. 2008. A first public consultation was held in 2009. A second public consultation is ongoing (until 13 May 2011). **A proposal of the Commission is scheduled for the 2nd quarter 2012**.

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Ethics and Marketing of medicinal products

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Regulatory Frame

- Medicinal products reviewed by the European Medicines Agency (EMEA)

The role of EMEA is to provide opinions on the basis of which the EC takes decisions regarding marketing authorisation for medicinal products. EMEA evaluates not only the effectiveness, safety and cost of the medical product but also the respecting of Good Clinical Practice, the granting of informed consent and of approval by ethical committees. When problems are identified, namely regarding ethical aspects, EMEA can advise the Commission to **refuse** the marketing authorisation or can advise the **withdrawal of marketing** authorisation already delivered by Member States**.** The EMEA intervention happens after the clinical trial is finalised and presented in the file and not before or during the trial.

Regulatory Frame

- Medicinal products reviewed by the European Medicines Agency (EMEA)

- Medicinal products reviewed by the European Medicines Agency (EMEA) can be granted a marketing authorisation by the Commission only if they are based on clinical trials conducted in compliance with the requirements of Directive 2001/20/EC and related implementing legislation. Article 3 of Commission Directive 2005/28/EC, in particular, lays down that clinical trials shall be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. **The EMEA has put in place a system of inspections of Good Clinical Practice in third countries since 2006. The inspection procedure has, among its priorities, the assessment of informed consent process and confirmation of ethics committee review.**

Ethics and EU funded clinical research

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Legal Basis in FP7 –

Seventh Framework Programme (Decision N 1982/2006/EC), Article 6 (1):

« All the research activities carried out under the Seventh Framework Programme shall be carried out in compliance with fundamental ethical principles. »

Rules for Participation, Article 10:

« A proposal […] which contravenes fundamental ethical principles […] shall not be selected . Such a proposal may be excluded from the evaluation and selection procedures at any time. »

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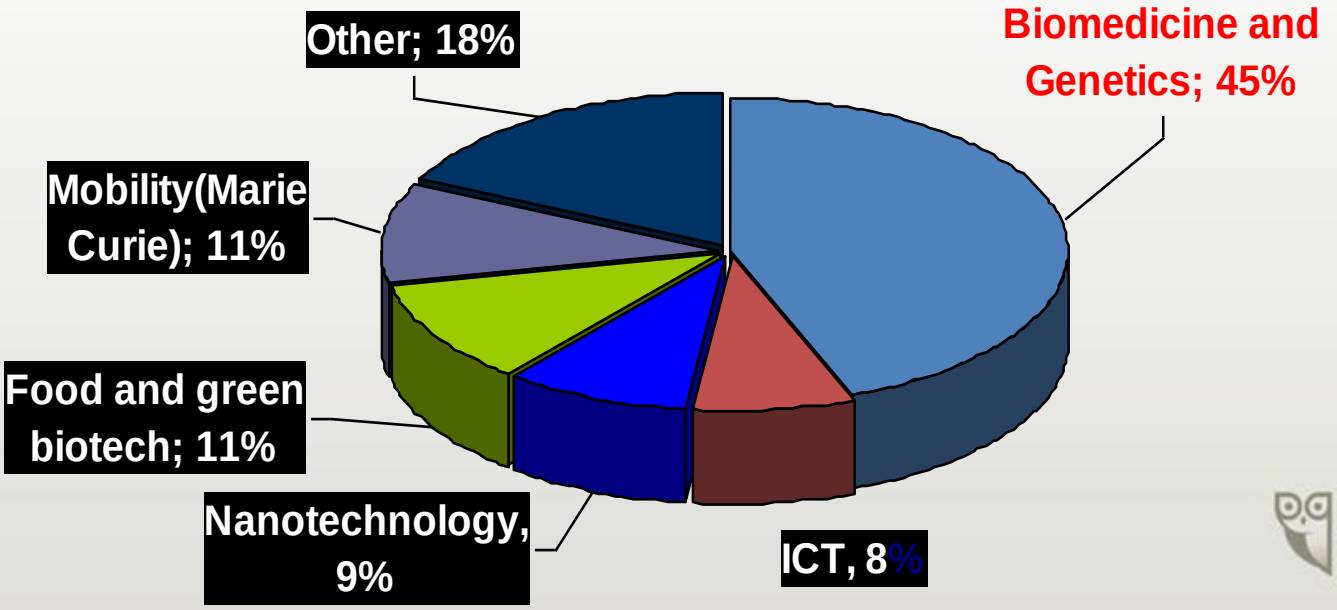
FP6 Proposals undergoing Ethical Reviews

11% of all funded FP6 projects have undergone an ethical review

Breakdown of projects having undergone ethical review, by research area



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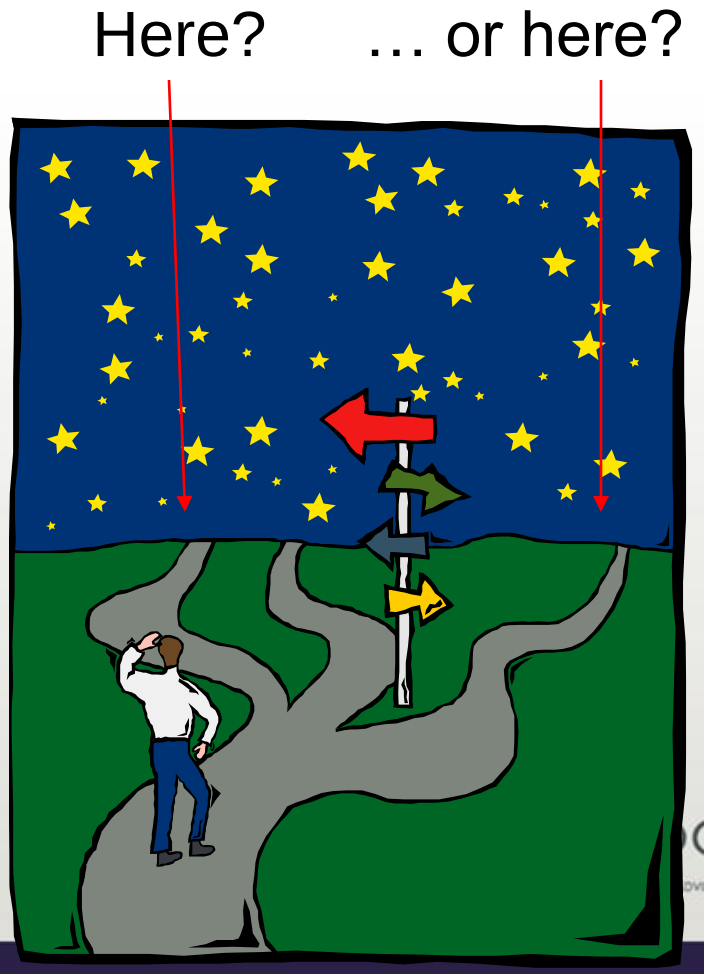
A responsible use of clinical trials would imply using governance tools in order to achieve the following: Protection of subjects participating in clinical trials; Information on clinical trials - including database; Good Manufacturing Practice (GMP); Good Clinical Practice (GCP). Why? How?

- Precondition of EU research funding
- Precondition of EU research authorisation
- Precondition of EU marketing
- Precondition of EU Patenting
- Monitored by Ethics audit, and inspectors.



Capacity Building on ethics in Developing Countries

The EC, following the remit on ethics stated in the Treaty, the EGE opinions, the EU regulative frame in clinical trials and FP7 'facilitates' local capacities rather than superimposing European standards.

This implies respect for local socio-cultural identities while promoting relevant documents existing at European and International level -e.g. the European charter of fundamental rights and the CoE bioethics convention.
The EC is therefore working in cooperation with other relevant bodies such as Unesco, WHO, CoE and non EU authorities.

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Ethical principles governing the conduct of clinical trials in the EU

- **Charter of Fundamental Rights of the European Union (2000)**
- **EGE Opinions**
- **the Council of Europe's Convention on Human Rights and Biomedicine (1997) and its Additional Protocol on Biomedical Research (2005),**
- **the Universal Declaration of Human Rights (1948),**
- **the Convention for the protection of Human Rights and fundamental Freedoms (1950),**
- **the United Nations' Convention on the Rights of the Child (1989),**
- **the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005),**
- **the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997),**
- **the International Declaration on Human Genetic Data (UNESCO, 2003),**
- **the CIOMS-WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects (Geneva 2002),**
- **the Declaration of Helsinki of the World Medical Association (2008),**
- **Opinion 17 of the European Group on Ethics(2003)**
- **the EU Ethical considerations for clinical trials on medicinal products conducted with paediatric population (2008).**
- **CPMP/ICH/135/95 guideline on Good Clinical Practice (1995) (ICH E6) and ICH E11**
- The European **pharmaceutical legislation** sets out the ethical requirements for the conduct of clinical trials in
- **Directive 2001/20/EC,**
- **Directive 2005/28/EC**
- **Directive 2001/83/EC.**
- Provisions of the European Paediatric Regulation **1901/06/EC**
- Provisions for the protection of personal data are laid down in Directive **1995/46/EC**

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A responsible use of clinical trials, where divergence may materialise?

- Provision for non commercialisation of the human body and its derivate
- Non profit involvement of volunteers (including tissue donation);
- Informed consent procedures
- data protection provisions
- benefit sharing
- open access
- protection of vulnerable groups
- accreditation of local RECs
- conflict of interest (sponsor)
- Training of REC members

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- Identify areas where soft-law will provide sufficient protection and areas where hard law is deemed necessarily
- Encourage professional responsibilities for individual researches and institutions;
- Facilitate and finance capacity building of REC in LDC
- Play a role in global governance to further strength the role of ethics in international clinical trials.

- The Commission has included protection of fundamental rights in all its policies
- FP7 finances ethics and R&D (DG RTD) and the Ethics review is a monitoring tool established by the EC.
- EU legislative framework safeguards subsidiarity in ethics while promoting values indicated in the Charter of fundamental rights

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See: EC page on clinical trials: http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm
Info on the future revision of EC/2001/20:
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